



Aalborg Universitet

AALBORG UNIVERSITY  
DENMARK

## Clinical outcomes following rhythm control for atrial fibrillation

*is early better?*

Kotalczyk, Agnieszka; Ding, Wern Yew; Gupta, Dhiraj; Wright, David Justin; Lip, Gregory Y H

*Published in:*  
Expert Review of Cardiovascular Therapy

*DOI (link to publication from Publisher):*  
[10.1080/14779072.2021.1902307](https://doi.org/10.1080/14779072.2021.1902307)

*Creative Commons License*  
CC BY-NC-ND 4.0

*Publication date:*  
2021

*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication from Aalborg University](#)

*Citation for published version (APA):*  
Kotalczyk, A., Ding, W. Y., Gupta, D., Wright, D. J., & Lip, G. Y. H. (2021). Clinical outcomes following rhythm control for atrial fibrillation: is early better? *Expert Review of Cardiovascular Therapy*, 19(4), 277-287.  
<https://doi.org/10.1080/14779072.2021.1902307>

### General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

### Take down policy

If you believe that this document breaches copyright please contact us at [vbn@aub.aau.dk](mailto:vbn@aub.aau.dk) providing details, and we will remove access to the work immediately and investigate your claim.

# Clinical outcomes following rhythm control for atrial fibrillation: is early better?

Agnieszka Kotalczyk, Wern Yew Ding, Dhiraj Gupta, David Justin Wright & Gregory Y. H. Lip

To cite this article: Agnieszka Kotalczyk, Wern Yew Ding, Dhiraj Gupta, David Justin Wright & Gregory Y. H. Lip (2021) Clinical outcomes following rhythm control for atrial fibrillation: is early better?, Expert Review of Cardiovascular Therapy, 19:4, 277-287, DOI: [10.1080/14779072.2021.1902307](https://doi.org/10.1080/14779072.2021.1902307)

To link to this article: <https://doi.org/10.1080/14779072.2021.1902307>



© 2021 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.



Published online: 13 Apr 2021.



Submit your article to this journal [↗](#)



Article views: 248



View related articles [↗](#)



View Crossmark data [↗](#)

REVIEW



## Clinical outcomes following rhythm control for atrial fibrillation: is early better?

Agnieszka Kotalczyk<sup>a,b</sup>, Wern Yew Ding<sup>a</sup>, Dhiraj Gupta<sup>a</sup>, David Justin Wright<sup>a</sup> and Gregory Y. H. Lip<sup>a,b,c</sup>

<sup>a</sup>Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; <sup>b</sup>Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Medical University of Silesia, Silesian Centre for Heart Diseases, Zabrze, Poland; <sup>c</sup>Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

### ABSTRACT

**Introduction:** An integral aspect of atrial fibrillation (AF) management involves better symptom control, incorporating a rate control, rhythm control, or a combination strategy. The 2020 ESC Guidelines suggest that rhythm control strategy should be recommended for symptomatic patients, to mitigate their symptoms and improve the quality of life. However, adequately powered randomized control trials and prospective ‘real-world’ registries are needed to fully assess the impact of early rhythm control strategies on clinical outcomes in patients with AF.

**Objective:** In this narrative review, we discuss clinical outcomes following rhythm management approach among patients with AF, considering the effectiveness of an early intervention strategy.

**Expert opinion:** Patients involvement and shared decision-making are crucial when deciding the optimal management strategy among patients with AF. For those with newly diagnosed symptomatic AF, an early invasive approach such as catheter ablation may have a role in preventing AF progression and subsequent pathophysiological changes.

### ARTICLE HISTORY

Received 4 January 2021  
Accepted 9 March 2021

### KEYWORDS

Atrial fibrillation;  
cardioversion; catheter  
ablation; heart failure; rate  
control; rhythm control

## 1. Introduction

Patients with atrial fibrillation (AF) have an increased risk of morbidity in terms of ischemic stroke and heart failure, and mortality compared to the general population [1]. AF is the most common sustained arrhythmia, with a predicted prevalence of 17.9 million in European adults by 2060 [2]. A new approach, incorporated in the latest 2020 European Society of Cardiology (ESC) guidelines on AF [3] – the Atrial fibrillation Better Care (ABC) pathway [4], was introduced to improve the outcomes of these patients [5,6]. In this pathway, ‘B’ focuses on better symptom control in patients with AF by utilizing either a rhythm or rate control strategy [4].

In general, a rhythm control strategy is reserved to mitigate symptoms and improve the quality of life [3]. Nonetheless, among a subset of patients with newly diagnosed AF (Table 1), an early intervention approach using catheter ablation may prevent further electrical and structural remodeling associated with disease progression. This is important as the restoration of sinus rhythm becomes increasingly more challenging with advanced disease states [3,7]. In this regard, a rate control strategy has not been shown to be beneficial to halt disease progression [6]. Therefore, there may be an argument for pursuing a rhythm control strategy in the first instance in patients with newly diagnosed AF. However, adequately powered randomized control trials (RCTs) and prospective ‘real-world’ registries are needed to fully assess the impact of early vs. late rhythm control strategies on clinical outcomes in patients with AF [3].

Due to the complexities of AF and the variety of treatment options available [8], adopting a highly individualized approach and shared decision-making process are crucial when optimizing the treatment of patients with AF (Table 2) [3,9,10]. Recently, new tools were developed to further improve AF management and research [3,11,12]. The 4S-AF scheme (Stroke risk, Symptom severity, Severity of AF burden, and Substrate for AF) provides a novel approach toward a pathophysiology-based characterization of patients with AF [11]. This model is applicable in daily clinical practice to support decision-making on stroke prevention, choice of rate or rhythm control, and management of comorbidities and risk factors [3,11]. Quality indicators have also been proposed to improve the quality of care in patients with AF [12].

In this narrative review, we provide an overview of the rhythm vs rate control strategies, different therapeutic options for rhythm control and benefits of an early rhythm control approach.

## 2. Rhythm vs. rate control strategy

Rhythm control in AF involves the restoration of sinus rhythm using ablation techniques, cardioversion or long-term treatment with anti-arrhythmic drugs, whereas rate control is aimed at allowing AF to persist but with well-controlled ventricular rates (Figure 1) [3,9,10]. In spite of decades of research, it has still not been demonstrated conclusively that rhythm control strategies are more effective than rate control in improving patients’ survival and clinical outcomes [13,14].

### Article highlights

- Highly individualized therapy and shared decision-making are crucial when deciding the optimal management strategy among patients with AF.
- Rhythm control strategy should be considered for symptomatic patients, to mitigate the symptoms and improve quality of life.
- Early rhythm control strategy, incorporated into holistic AF care, may prevent AF progression and improve outcomes among selected patients with newly diagnosed AF.
- Further randomized control trials and 'real world' registries are needed to assess the impact of early rhythm control strategy on long-term clinical outcomes in patients with AF.

**Table 1.** Classification of atrial fibrillation [3].

| AF type                     | Description  |
|-----------------------------|--|
| First diagnosed AF          | <ul style="list-style-type: none"> <li>• Not diagnosed before</li> <li>• Irrespective of AF-duration</li> </ul>  |
| Paroxysmal AF               | <ul style="list-style-type: none"> <li>• Episodes terminated spontaneously or with intervention &lt;7 days from AF-onset</li> </ul>  |
| Persistent AF               | <ul style="list-style-type: none"> <li>• Episodes sustained <math>\geq 7</math> days of AF-onset</li> <li>• Episodes terminated by cardioversion after <math>\geq 7</math> days of AF-onset</li> </ul> |
| Long-standing persistent AF | <ul style="list-style-type: none"> <li>• Continuous episode &gt;12 months' duration, when a rhythm control strategy is adapted</li> </ul>  |
| Permanent AF                | <ul style="list-style-type: none"> <li>• AF accepted by the patient and physician</li> <li>• No further attempts to restore/maintain sinus rhythm</li> </ul>   |

AF – atrial fibrillation

**Table 2.** Factors favoring rate or rhythm control strategies among patients with AF [3,6,7].

| Rate control                            | Rhythm control                           |
|---|--|
| Older age                               | Younger age                              |
| Comorbidities                           | Tachycardia-mediated cardiomyopathy      |
| Asymptomatic AF                         | Symptomatic AF                           |
| Therapy after failure of rhythm control | Rate control difficult to achieve        |
| Long standing persistent AF             | 1 <sup>st</sup> AF episode/Paroxysmal AF |
| <b>Patient's preferences</b>            |  |
| <b>Shared-decision making</b>           |  |

AF – atrial fibrillation

In the AFFIRM study, which was a RCT comparing rhythm and rate control strategies among 4060 patients with AF, it was found that the rhythm-control strategy offered no survival advantage (mortality at five years: 23.8% vs. 21.3% with rate control;  $P = 0.08$ ) and was related to more adverse drug effects [15]. The study, published in 2002, predated the advent of catheter ablation, and warfarin discontinuation rates were particularly high in the rhythm control arm. Indeed, a sub-analysis of the trial showed that the presence of sinus rhythm and the use of warfarin was associated with a lower risk of death [16].

The EORP-AF Pilot Registry was conducted in nine European countries to assess contemporary management of patients with AF [17]. The influence of a rate vs. rhythm control strategy in 3119 real-world patients over a 1-year follow-up was reported. It was found that 1036 (33.2%) patients were managed with rate control only and 355 (11.4%) patients with rhythm control only. The most commonly used drug for rate

control was beta-blockers, while amiodarone was the most frequent anti-arrhythmic drug. Patients assigned to a rhythm control strategy were younger and more likely to be male. The authors demonstrated that a rhythm control strategy was independently related to a lower risk of adverse events and all-cause mortality at 1-year follow-up [17]. Likewise, the results of Get With The Guidelines-Heart Failure registry which included patients with AF and heart failure with preserved left ventricular function showed a lower rate of all-cause death at one year in the rhythm control group, as compared with the rate control group (30.8% vs. 37.5%,  $P < 0.01$ ; HR: 0.86; 95% CI: 0.75–0.98) [18]. A meta-analysis of 10 RCTs indicated that among young AF patients (aged <65 years), rhythm control may be preferable strategy, resulting in a higher rate of restoration of sinus rhythm, and a lower risk of all-cause mortality and worsening heart failure as compared to rate control strategy [19].

However, an RCT among patients with a recurrence of persistent AF showed that rate control was not inferior to rhythm control for the prevention of cardiovascular-related morbidity and all-cause death [20]. Likewise, the ORBIT-AF Registry, consisting of 9749 patients with AF found that rhythm control was not superior to rate control strategy, but was related to a higher risk of cardiovascular hospitalizations (HR: 1.24; 95% CI: 1.10–1.39) [21].

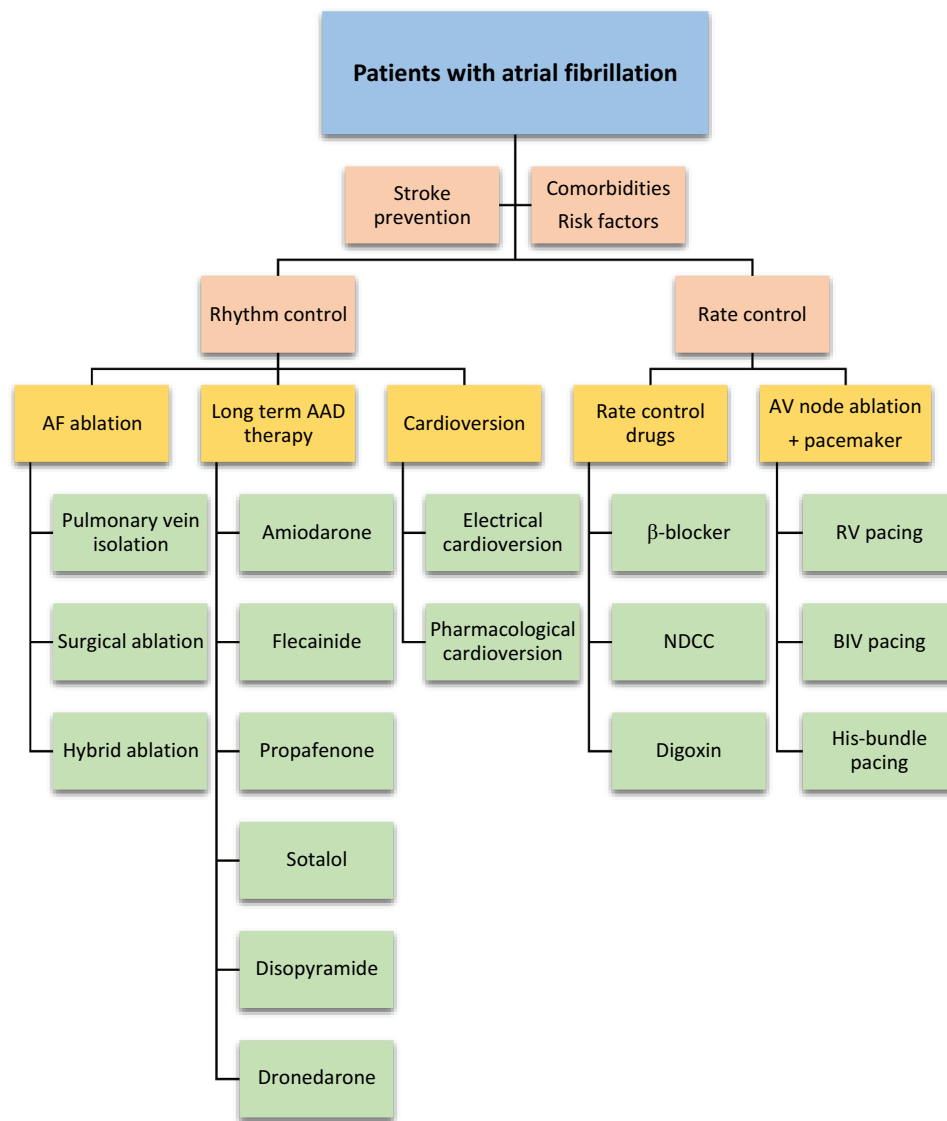
Nonetheless, major limitations of the studies described above are that they relied primarily on the use of anti-arrhythmic drugs which are known to perform poorly in maintaining long-term sinus rhythm and are often associated with significant side effects. Therefore, it begs the question as to whether the results would have been different if we analyzed only the subgroup of patients with successful anti-arrhythmic treatment or if we utilized a different approach such as AF ablation which has been shown to have better success rates than drugs.

### 3. Medical therapy vs. AF ablation

Over the past two decades, the field of AF ablation has received much attention. At present, the cornerstone of AF catheter ablation is electrical isolation of the pulmonary veins (PVI) [22]. This has been associated with good long-term outcomes in maintaining sinus rhythm with low rates of procedural complications [23,24].

#### 3.1. General AF population

The CABANA trial was a recently published RCT, including 2204 patients with paroxysmal or persistent AF with a median age of 68 years, comparing outcomes of catheter ablation vs. antiarrhythmic drug therapy [25]. Patients had a median time since AF onset of 1.1 years, and more than half the patients had non-paroxysmal AF. Over a median follow-up of 48.5 months, the use of catheter ablation did not significantly reduce the combined primary endpoint of death, disabling ischemic stroke, major bleeding, or cardiac arrest (8.0% vs 9.2%; HR: 0.86; 95% CI: 0.65–1.15). The risk of death or cardiovascular hospitalization (HR: 0.83; 95% CI: 0.74–0.93) and the risk of AF recurrence (HR: 0.52; 95% CI: 0.45–0.60) was



**Figure 1.** General management strategy among patients with atrial fibrillation AV – atrioventricular; AF – atrial fibrillation; NDCC – Non-dihydropyridine calcium channel blocker; AAD – antiarrhythmic drug; RV – right ventricular; BIV – biventricular. Based on Refs [3,4,9,10].

significantly lower in the ablation group as compared to the drug therapy group [25]. However, almost 10% patients randomized to the catheter ablation group did not undergo the procedure, whereas 27.5% of patients assigned to the drug therapy group received catheter ablation. Such significant cross-over may have introduced bias to the results and in fact, the ‘as-treated’ analysis demonstrated catheter ablation to be superior to medical therapy. Indeed, a subsequent ‘real-world’ study revealed that catheter ablation was related to a reduction in the composite endpoint of death, disabling ischemic stroke, major bleeding, or cardiac arrest (HR: 0.75; 95% CI: 0.70–0.81); and that the benefit was more significant in the CABANA-eligible patients (HR 0.70, 95% CI 0.63–0.77) compared with the medical therapy group [26].

Notably, a meta-analysis of nine studies assessed the long-term outcomes of catheter ablation vs. medical therapy alone in a general AF population ( $n = 241,372$ ) [27]. During a follow-up of 3.5 years, catheter ablation significantly

reduced the risk of death (HR: 0.62; 95% CI: 0.54–0.72), stroke (HR: 0.63; 95% CI: 0.56–0.70), and hospitalization (HR: 0.64; 95% CI: 0.51–0.80) as compared to the medical therapy [27].

Likewise, a study of 2,720 patients with AF who underwent an ablation assessed the impact of the procedure on recurrent hospitalizations [28]. AF ablation was related to a 35% decline in all-cause hospitalizations (from 1,669 hospitalizations in the year pre-ablation to 1,034 hospitalizations in the year post-ablation), which was driven by a reduction in hospitalizations for AF and heart failure (a reduction of 56% and 43%, respectively) [28]. The independent predictors for decreased AF hospitalization were age <55 years, history of obstructive sleep apnea and heart failure [28]. Furthermore, catheter ablation significantly increased the time to first recurrence of atrial arrhythmias among patients with paroxysmal and persistent AF, during the 12-year follow-up period in comparison to antiarrhythmic drugs [29].

**Table 3.** The AFFIRM trial vs. the EAST-AFNET 4 trial.

|  | AFFIRM [15]     | EAST-AFNET 4 [43]   |
|--|-----------------|---|
| Era when patients were recruited       | 1995–2002       | 2011–2016   |
| Mean age of patients [years]           | 69.7 ± 9.0      | 70.2 ± 8.4  |
| Absence of symptoms (%)                | 6               | 30  |
| Mean Time since AF diagnosis [days]    | 42              | 36  |
| Mean Left atrial size (cm)             | 4.3 ± 0.8       | 4.4 ± 0.9   |
| Composite primary end point            | All-cause death | Death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome |
| OAC discontinuation rates [%]          | 15              | 3.2   |
| SR maintenance rates in rhythm arm [%] | 62.6            | 82.1  |
| Ablation utilization [%]               | 0.7             | 19.4  |
| Structured follow up [years]           | 3.5             | 5.1   |

AF – atrial fibrillation; OAC – oral anticoagulant; SR – sinus rhythm

**Table 4.** Factors adversely affecting outcomes of catheter ablation [3,58–63].

| Factors adversely affecting outcomes of catheter ablation              |
|--|
| -Non-paroxysmal AF   |
| -AF duration > 6 years   |
| -Age > 75 years  |
| -Female sex  |
| -Left atrial volume indexed to body surface area >34 ml/m <sup>2</sup> |
| -Atrial dilatation > 50 mm   |
| -Structural heart disease  |
| -Obesity   |
| -Sleep apnea   |
| -Chronic kidney disease (GFR <60 ml/min/1.73 m <sup>2</sup> )          |

AF – atrial fibrillation; GFR – glomerular filtration rate

Another study assessed the risk of ischemic stroke and intracranial hemorrhage among patients with AF, depending on the treatment strategy [30]. At 51 months of follow-up, 35.8% of patients with catheter ablation had an AF recurrence, and 29.7% of these patients underwent a repeat procedure. It was found that the risk of ischemic stroke was significantly higher in the group treated with medical therapy as compared to the catheter ablation group and the non-AF group (Incidence Rate Ratio [IRR]: 1.09% vs 0.30% vs 0.34%; respectively). Of note, among those remaining in sinus rhythm after ablation, the risk of stroke was lower than in patients with post-ablation AF recurrences (IRR: 0.87% vs 0.24%). Curiously, the authors reported that the risk of intracranial bleeding was lower in the ablation group than in the medical therapy group (IRR: 0.06% vs. 0.17%); and that the risk of intracranial bleeding did not differ between the ablation group and the non-AF group [30]. In this regard, it seems implausible that catheter AF ablation would directly influence the risk of ICH, suggesting that there may be potential bias in the study [31]. A separate analysis using the same database of patients with AF showed that catheter ablation was related to a lower incidence and risk of dementia, including Alzheimer's disease and vascular dementia (HR: 0.73; 95% CI: 0.58–0.93) compared with patients with medical therapy during a follow-up of 52 months [32].

### 3.2. Patients with atrial fibrillation and heart failure

CASTLE-AF was an RCT assessing the outcomes among patients with symptomatic paroxysmal or persistent AF and

symptomatic heart failure (left ventricular ejection fraction ≤35%) with an implanted cardioverter-defibrillator, and a history of unsuccessful [or unwillingness to take] antiarrhythmic drug therapy [33]. Patients were randomized to catheter ablation or standard medical therapy. A significantly lower rate of a composite endpoint of all-cause death or hospitalization for worsening heart failure was observed among those in the ablation group as compared to the drug therapy group (28.5% vs 44.6%; HR: 0.62; 95% CI: 0.43–0.87); catheter ablation was also related to a lower burden of AF, increased the 6-min walking distance, and improved the left ventricular ejection fraction [33]. However, only a minority of patients who were initially screened for the trial were found to be eligible. Indeed, a study [34] assessing the generalizability of CASTLE-AF showed that only 7.8% of patients in routine practice would have met the inclusion criteria for the CASTLE-AF. Nonetheless, this study found that patients in the catheter ablation group had a lower risk of the primary outcome as compared to standard medical therapy (HR: 0.81; 95% CI: 0.76–0.87) [34].

A meta-analysis of seven RCTs among patients with AF and heart failure showed that catheter ablation was associated with a significant reduction in mortality (risk ratio [RR]: 0.50; 95% CI: 0.34–0.74) and hospitalizations for heart failure (RR: 0.56; 95% CI: 0.44–0.71); and led to improvements in left ventricular ejection fraction (weighted mean difference: 7.48; 95% CI: 3.71–11.26) as compared to medical therapy [35]. Nonetheless, it is important to note that the inclusion and exclusion criteria differed between the analyzed studies.

Overall, a rhythm control strategy with anti-arrhythmic drugs is not superior to rate control in terms of mortality and clinical outcomes [15]. However, catheter AF ablation may have a positive effect on all-cause mortality, risk of stroke, re-hospitalization, cognitive function, and quality of life among patients with paroxysmal and persistent AF as compared to medical therapy, especially in specific subgroups [29,30,32,36]. Patients with 'long-standing persistent' AF (>3 years continuously in AF prior to ablation) are less likely to restore and maintain the sinus rhythm post ablation than



those with paroxysmal AF [37]. Of note, time since the first AF episode and heart failure are associated with higher, whereas the absence of structural heart disease, with lower AF recurrences after catheter ablation [38]. A 10-year post AF ablation follow-up of 255 patients showed that greater LA anteroposterior diameter, hypertension, higher BMI and increased fasting blood glucose were independently associated with AF recurrences [39].

Given the current literature, patient selection, and preferences are important aspects of treatment, including the benefit-risk assessment of ablation in order to identify an optimal individualized strategy [40]. Further studies are needed to determine whether there are additional subgroups who may benefit from AF ablation in terms of reducing long-term complications and improving survival.

#### 4. Early rhythm control

Early intervention in the 'natural history' of AF may prevent its progression and AF-related pathophysiological changes [41]. New management strategies are proposed to maintain sinus rhythm in the 'early-stage' AF and improve clinical outcomes in patients with AF [42].

The recently published EAST-AFNET 4 trial included 2789 patients with AF diagnosed up to one year prior to enrollment; which was symptomatic in around 70% of patients [43]. Patients were randomized to early rhythm control (treatment with antiarrhythmic drugs or AF ablation) or usual care (rhythm control was limited to the symptomatic patients). The primary composite outcome was cardiovascular-related death, stroke, or cardiovascular-related hospitalization; and the primary composite safety outcome was death, stroke, or serious adverse events related to rhythm control therapy. The trial was discontinued after a median of 5.1 years of follow-up due to the demonstration at the third interim analysis that early rhythm control therapy was related to a lower risk of adverse cardiovascular outcomes than usual care. The first-primary-outcome event rate was 3.9 per 100 person-years in the early rhythm control group vs 5.0 per 100 person-years in the usual care group (HR: 0.79; 96% CI: 0.66–0.94), while the primary safety outcome did not differ significantly between the groups. The use of oral anticoagulation (OAC) was continued during the follow-up (although data on quality of anticoagulation were not reported), and the incidence of ischemic stroke was low in both groups (0.6% in the early rhythm control group and 0.9% in the usual care group). Of note, sinus rhythm at 24 months was maintained in 82% of the patients assigned to early rhythm control and 60% of patients in the usual care group [43]. It is important to note that only around one in five patients in the rhythm control arm underwent catheter ablation during the study period, with antiarrhythmic drugs being the predominant mode of rhythm control. 14.6% of patients in the usual care group too received the rhythm control therapy to mitigate their symptoms. Given that patients in the early rhythm control group underwent an intense, structured follow-up, the positive results may have been influenced by better treatment of risk factor and comorbidities in the intervention arm [44]. As shown in Table 3, there are important differences between the AFFIRM and EAST-

AFNET4 trials, which may explain the different headline results. In particular, the success rate of the rhythm control strategy was significantly higher in EAST-AFNET4, and the OAC discontinuation rates significantly lower than in AFFIRM. In summary, EAST-AFNET four suggests that early rhythm control is a reasonable consideration as part of a holistic approach to AF care [3,45].

A decade ago, the MANTRA-PAF study [46] was performed to evaluate the outcomes of radiofrequency ablation as first-line therapy for patients with paroxysmal AF. Patients were randomized to receive radiofrequency catheter ablation or treatment with anti-arrhythmic drugs. Primary end points were the cumulative and per-visit burden of AF assessed in 7-day Holter-ECG (at 3, 6, 12, 18, and 24 months). Although there was no significant difference between groups in the cumulative burden of AF, the AF burden at 24 months, was significantly lower in the ablation group than in the AAD group (9% vs. 18%;  $P = 0.007$ ); and more patients in the ablation group were free from symptomatic AF (93% vs. 84%;  $P = 0.01$ ) [46].

Results of two RCTs, evaluating cryoballoon AF ablation as a first-line strategy compared with anti-arrhythmic drug therapy: the STOP-AF FIRST [47] and the EARLY-AF [48] have been recently published. The trials comprised of patients with symptomatic, paroxysmal AF untreated previously with rhythm-control strategy, and without severe left atrial enlargement (diameter <5 cm) [47,48]. Both studies showed that cryoballoon ablation had a superior efficacy as first-line therapy as compared to antiarrhythmic drugs (class I or III agents) during 12 months of follow-up [47,48]. The primary efficacy outcome of the STOP-AF FIRST was defined as the freedom from efficacy failure, i.e. acute procedural failure, any subsequent AF surgery or ablation, atrial arrhythmias or cardioversion (and antiarrhythmic drug therapy in the ablation group) after the 90-day blanking period [47]. It occurred in 75% of patients from the cryoballoon ablation group and in 45% of those from the antiarrhythmic drug therapy group [47]. Limitations of the study include arrhythmia assessment with intermittent electrocardiography monitoring, possibly inadequate drug dosing in the drug therapy arm (the drug failures were observed mostly among patients taking very low doses), and a 15% rate of crossover from drug therapy arm to the ablation group which counted as a component of the primary efficacy outcome [47]. On the other hand, EARLY-AF study was methodologically more sound, in that there was no crossover from the drug therapy to the ablation group, and there was continuous rhythm monitoring with an implantable loop recorder. As such, the results of EARLY-AF study [48] may be more representative of the true benefits of catheter ablation: atrial tachyarrhythmia occurred in 43% of patients in the ablation group and in 68% of those from the antiarrhythmic drug therapy (HR: 0.48; 95% CI: 0.35–0.66). 11% of patients in the ablation arm had symptomatic post-ablation atrial tachyarrhythmia vs. 26.2% of those from the antiarrhythmic drug therapy (HR: 0.39; 95% CI: 0.22–0.68), and this was associated with better QOL improvements and lower incidence of hospitalization on follow up [48].

The recently presented Cryo-FIRST Cryoballoon Ablation Trial (NCT01803438) [49] among naïve patients with AF

similarly showed a higher arrhythmia-free survival rate among patients after cryoballoon ablation as compared to the anti-arrhythmic drugs therapy group (82.2% vs. 67.6%) during 12 months of follow-up [50]. In addition, an improvement in the quality of life was observed in the catheter ablation group; and 86.5% of the these patients were symptom-free vs. 70.4% of patients in the anti-arrhythmic drug group [51]. Of note, the results of ATTEST trial [52] support the notion of increased benefit with AF catheter ablation as compared to AAD therapy. The study assessed the AF progression among patients with paroxysmal AF, randomized to radiofrequency ablation or AAD treatment. At 3 years, the rate of persistent AF/atrial tachycardia was significantly lower in the ablation group compared with the AAD therapy group (2.4% vs. 17.5%;  $P = 0.0009$ ). It was found that patients aged  $\geq 65$  years were more likely to progress to persistent arrhythmia than those aged  $< 65$  years (HR: 3.87; 95% CI: 0.88–17.00) [52].

A recent European multicentre registry [53] showed that cryoballoon ablation may be useful as a first-line option even for patients with persistent AF. At 24 months, the arrhythmia-free survival rate was 64% of patients with persistent AF and 57% of those with long-standing persistent AF. Repeat procedures were required in 20% of those with persistent AF and in 32% of subjects with long-standing persistent AF.

A study [54] among 1241 patients showed that the time interval between AF diagnosis and ablation was associated with procedural outcomes. It found that the shorter diagnosis-to-ablation time of less than 1 year was related to a lower rate of AF recurrence, and a reduction in atrial remodeling biomarkers, i.e. B-type natriuretic peptide, C-reactive protein, and left atrial size as compared to those with the longer diagnosis-to-ablation time [54]. Thus, early ablation-based rhythm control may prevent cardiac remodeling, thereby translating to physiological and symptomatic improvement, in particular among patients with AF and tachycardia-mediated cardiomyopathy [55].

Given the significant upfront costs of catheter ablation, the cost-effectiveness of using it as first-line therapy needs to be evaluated. A subanalysis [56] of the MANTRA-PAF trial was performed to estimate the cost-effectiveness of radiofrequency catheter ablation for paroxysmal AF as first-line treatment, compared with antiarrhythmic drugs during the 2-year follow-up. Radiofrequency catheter ablation was found to be a cost-effective strategy in younger patients (€3434/quality-adjusted life years [QALY] in  $\leq 50$ -year-old patients vs. €108 937/QALY in  $> 50$ -year-old patients) [56]. It should be noted that in the MANTRA-PAF trial, almost half the patients in the ablation arm required repeat procedures, whereas the corresponding figure in the recent cryoballoon trials was around 1 in 10. This, along with the much shorter procedure times with Cryoballoon as compared to radiofrequency ablation [57], means that cost-effectiveness of cryoballoon PVI as first-line treatment can be expected to be even higher.

The use of an early rhythm control strategy may reduce AF-related adverse clinical outcomes among patients with recently diagnosed AF. For this purpose, catheter ablation as first-line treatment may be a safe and effective approach, with superior results compared to anti-arrhythmic drugs. However, the long-term impact on heart failure and mortality has not

been studied; and prognostic implications of this strategy require further confirmation in RCTs and 'real-world' studies.

## 5. Factors adversely affecting outcomes of catheter ablation

Several scores, stratifying the risk of adverse outcomes or AF recurrence among patients undergoing AF catheter ablation, have been developed. (Table 4) [3,58–60]. The validity of these scores requires further confirmation in large cohort studies; and the use of biomarkers or cardiovascular imaging may improve their predictive value. Besides the evaluation of the predictors of AF recurrence, the personalized approach, including the patient's preferences, should be adjusted [3,61].

Left atrial volume was shown to be the most important independent predictor of AF recurrence post-ablation [62]. A pooled meta-analysis of 7217 patients who underwent AF ablation showed a 31.2% AF recurrence rate during a follow-up of 22 months [63]. Patients with persistent AF had a greater risk of arrhythmia recurrence after the first ablation (OR 1.78; 99% CI: 1.14–2.77) than these with paroxysmal AF. In the overall population, the strongest predictors of AF ablation failure were an early ( $> 30$  days) AF recurrence (OR: 4.30; 95% CI: 2.00–10.80), a left atrial diameter  $> 50$  mm (OR: 5.10; 95% CI: 2.00–12.90), and valvular AF (OR: 5.20; 95% CI: 2.22–9.50) [63].

## 6. Conclusions

The management of AF should be individualized with a shared decision-making process in order to determine the optimal rhythm or rate control strategy to pursue. The benefit of anti-arrhythmic drugs compared to rate control options remains unproven. However, there is emerging evidence that catheter AF ablation may be more effective than rate control alone in improving the patients' QOL, and clinical outcomes. As such, an early rhythm control strategy using catheter ablation may be a promising approach among patients with newly diagnosed paroxysmal AF when recommended as part of holistic care.

## 7. Expert opinion on the future of AF management

Rhythm control involves AF ablation, cardioversion or long-term treatment with anti-arrhythmic drugs to maintain sinus rhythm; which should be recommended for symptom relief and to improve quality of life(3).

Historically, acute peri-procedural complications occurred in 4.8–7.8% of patients undergoing AF ablation, including tamponade, stroke, or transient ischemic attack, and death ( $< 0.1\%$ ) [25,64–66]. During long-term follow-up, re-ablation was required in 20–50% of patients [67,68]. However, more recent studies have not only shown a much lower risk of major complications ( $< 2\%$ ), but also a significantly lower need for repeat procedures ( $< 20\%$ ) [25,47,48]. Also, a small subset of patients with persistent and long-standing AF may benefit from a hybrid approach, integrating the strengths of both surgical and catheter ablation [69,70]. There are also limited data regarding AF ablation and left atrial appendage occlusion performed as a single procedure; to integrate the 'cure' for AF



and prevent stroke complications, in order to avoid the risk associated with repeated procedures [71–73].

Given the current evidence-base, rhythm control may be the preferred option among patients with AF and acute heart failure; and for unstable patients, an urgent cardioversion should be considered [74]. In this setting, all anti-arrhythmic agents apart from amiodarone, are contraindicated. Therefore, electrical cardioversion should be considered as it restores sinus rhythm faster and also more effectively than pharmacological cardioversion with amiodarone [74]. It is important that thromboembolic risk should be assessed and an OAC initiated prior to the procedure. In those at increased risk of stroke, the OAC should be continued lifelong [75]. A study among 5625 patients with AF and acute heart failure showed that successful restoration of sinus rhythm was related to a significantly lower rate of all-cause mortality (HR: 0.68; 95% CI: 0.49–0.93), heart failure re-hospitalization (HR: 0.66; 95% CI: 0.45–0.97) as compared to persistent AF, during 2.6 years of follow-up [76]. Notably, most patients with recent-onset AF will convert spontaneously within 48 hours, and a wait-and-see approach may be reasonable in stable patients [75,77].

First and foremost, it is crucial to assess and treat comorbidities. A position paper on the prevention of AF highlighted that avoidable or modifiable risk factors are related to lifestyle choices, e.g. diet modification, quitting smoking and alcohol, regular physical activity [78]. Hence, as clinicians, we should direct our focus toward specific at-risk groups such as adolescents who, paradoxically, are at increased cardiac risk due to the epidemics of obesity, inadequate nutrition, smoking and alcohol abuse [78,79]. Of note, obesity [and male gender] were independent predictors of failed cardioversion [80], whereas weight-loss was related to the maintenance of sinus rhythm [81]. Likewise, the RACE 3 was a RCT of 245 patients with early persistent AF and mild-to-moderate heart failure randomized to the targeted therapy of underlying conditions or conventional therapy [82]. Both groups received standard treatment of AF and heart failure, and rhythm control therapy. At one-year follow-up, the improvement in blood pressure, lipid profile, weight and heart failure was observed in the intervention group. Besides, sinus rhythm was present in 75% of patients with targeted therapy vs. 63% in the conventional group (odds ratio [OR]: 1.76; 95% CI: 1.02–3.05) [82].

Likewise, impressive progress in the field of the electrophysiology has led to improvements of existing techniques and tools, and new ones are constantly emerging, increasing the efficacy and safety of catheter AF ablation [83,84]. Of note, the randomized trials (e.g. CIRCA-DOSE, FIRE and ICE) directly comparing cryoballoon vs. radiofrequency ablation did not find one energy source superior to the other [85,86]. In addition, point-by-point radiofrequency ablation developed significantly during last decade (introduction of contact force catheters, ablation indexes). It is expected that single-shot PVI ablation will enable quicker and more durable ablation lesion sets [84,87]. Moreover, advances in electroanatomical mapping technologies have provided a better understanding of the triggers for AF, outside of the pulmonary veins [88]. With the integration of these AF mapping systems, specific targets for ablation may be identified, resulting in better AF control beyond PVI alone [84,89]. More recently, the most

promising new technology in catheter AF ablation is pulsed-field ablation (PFA) [90]. This technique is used to create micropores at the cell membranes to ablate myocardium without tissue heating [91]. The IMPULSE (NCT03700385) and the PEFCAT (NCT03714178) were the first human trials on PFA, presenting excellent efficacy and safety data. PFA was reported to be an ‘ultrafast’ procedure with a 100% efficacy in terms of 3-month durability of PVI [92]. Additionally, early studies with electroporation show very promising high success rate and low complication rate. Thus, catheter ablation is a procedure that comprises different approaches, which are continuously evolving.

Complementary data on the identification and monitoring of AF can be seen in the use wearable technology and implantable loop recorders to detect and record AF episodes [93–97]. Indeed, smartwatches may be used for long-term AF screening in large populations, especially in high-risk patients. Early AF detection and implementation of proper therapy may reduce the risk of AF-related complications [98]. A recent study showed that patients with pre-ablation AF episodes lasting less than 24 hours (continuously) had a significantly lower incidence of arrhythmia recurrence following AF ablation compared to those with AF pre-ablation episodes of between two and seven days, and those with episodes for more than seven days (0% vs. 0.1% vs. 1.0%; respectively) [99]. Thus, wearable technology may be a useful tool to assess the burden of AF for risk stratification pre-ablation. Furthermore, it can be used to monitor for AF recurrences during long-term follow-up. Regular post-ablation follow-up is crucial to implement appropriate and effective rhythm control therapy, assess symptoms, and detect and optimize treatment of concomitant risk factors and comorbidities [98,100–105]. Overall, the wearable technology may assist in integrated care, optimizing the holistic approach among patients with AF [106].

## Declaration of interest

G Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. D Gupta has received institutional research grants from Boston Scientific, Medtronic and Biosense Webster, and personal advisory fees from Boehringer Ingelheim, Boston Scientific and Abbott. D Wright has received research grants and consultancy fees from Boston Scientific and Medtronic.

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

## Disclosures statement

No potential conflict of interest was reported by the author(s).

## References

- Papers of special note have been highlighted as either of interest (\*) or of considerable interest (\*\*) to readers.
1. Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study.

- Circulation [Internet]. 2014;129:837–847. [cited 2020 Nov 7] Available from: [/pmc/articles/PMC4151302/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/25111111/)
2. Krijthe BP, Kunst A, Benjamin EJ, et al. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* [Internet]. 2013;34:2746–2751. Available from: <https://doi.org/10.1093/eurheartj/ehz280>.
  3. Hindricks G, Potpara T, Dagres N, et al. ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS): the Task Force for the diagnosis and management of atrial fibrillation of the European. *Eur Heart J* [Internet]. 2020;2020 [cited 2020 Mar 10]; Available from: <https://doi.org/10.1093/eurheartj/ehaa612>. • **The novel ESC Guidelines for the management of AF patients.**
  4. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol*. 2017;14:627–628. • **The new holistic approach for AF management.**
  5. Yoon M, Yang PS, Jang E, et al. Improved population-based clinical outcomes of patients with atrial fibrillation by compliance with the simple ABC (Atrial Fibrillation Better Care) pathway for integrated care management: a nationwide cohort study. *Thromb Haemost* [Internet]. 2019 [cited 2020 Dec 7];19:1695–1703. Available from: <http://www.thieme-connect.de/DOI/DOI?10.1055/s-0039-1693516>
  6. Ding WY, Lip GYH, Potpara TS. Atrial fibrillation: can it be as easy as CC to ABC? *Eur J Clin Invest* [Internet]. 2020 [cited 2020 Dec 7];50. Available from: <https://onlinelibrary.wiley.com/doi/10.1111/eci.13413>
  7. Bunch TJ, May HT, Bair TL, et al. Increasing time between first diagnosis of atrial fibrillation and catheter ablation adversely affects long-term outcomes. *Hear Rhythm* [Internet]. 2013 [cited 2020 Nov 7];10:1257–1262. Available from: <http://www.heart-rhythmjournal.com/article/S1547527113005511/fulltext>
  8. De Caterina R, Ageno W, Agnelli G, et al. The Non-Vitamin K Antagonist Oral Anticoagulants in Heart Disease: section V-Special Situations [Internet]. *Thromb. Haemost. Georg Thieme Verlag*. 2019; [cited 2020 Dec 8]. p. 17–38. Available from: <http://www.thieme-connect.de/DOI/DOI?10.1055/s-0038-1675816>
  9. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest* 2018;154:1121–1201.
  10. January CT, Wann LS, Calkins H, et al. AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the american college of cardiology/american heart association task force on clinical practice guidelines and the heart rhythm society in collaboration with the society of thoracic surgeons. *Circulation* [Internet]. 2019;140:e125–e151. 2019 [cited 2020 Mar 10]; Available from: <https://www.ahajournals.org/doi/10.1161/CIR.0000000000000665>
  11. Potpara TS, Lip GYH, Blomstrom-Lundqvist C, et al. The 4S-AF scheme (stroke risk; symptoms; severity of burden; substrate): a novel approach to in-depth characterization (rather than classification) of atrial fibrillation. *Thromb Haemost* [Internet]. 2020 [cited 2020 Sep 9]; Available from: <http://www.ncbi.nlm.nih.gov/pubmed/32838473>.
  12. Arbelo E, Aktaa S, Bollmann A, et al. Quality indicators for the care and outcomes of adults with atrial fibrillation. *Europace* [Internet]. 2020; Available from: <https://doi.org/10.1093/europace/ehaa253>.
  13. Sankaranarayanan R, Kirkwood G, Visweswariah R, et al. How does chronic atrial fibrillation influence mortality in the modern treatment Era? *Curr Cardiol Rev* [Internet]. 2015 [cited 2020 Nov 7];11:190–198. Available from: [/pmc/articles/PMC4558350/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/25111111/).
  14. Zhang YY, Qiu C, Davis PJ, et al., Predictors of progression of recently diagnosed atrial fibrillation in REGISTRY on cardiac rhythm Disorders assessing the control of atrial fibrillation (RecordAF)-United States cohort. *Am J Cardiol* [Internet]. Elsevier; 2013 [cited 2020 Nov 7]. p. 79–84. Available from: [www.ajconline.org/http://dx](http://www.ajconline.org/http://dx)
  15. Wyse DG, Waldo AL, DiMarco JP, et al. A Comparison of Rate Control and Rhythm Control in Patients with Atrial Fibrillation. *N Engl J Med* [Internet]. 2002;347:1825–1833. [cited 2020 Nov 8]; Available from: [www.nejm.org](http://www.nejm.org)
  16. Epstein AE. Relationships between sinus rhythm, treatment, and survival in the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) study. *Circulation* [Internet]. [cited 2020 Nov 8];109:1509–1513. Available from: <https://www.ahajournals.org/doi/10.1161/01.CIR.0000121736.16643.11>
  17. Purmah Y, Proietti M, Laroche C, et al. Rate vs. rhythm control and adverse outcomes among European patients with atrial fibrillation. *Europace* [Internet]. 2018;20:243–252. Available from: <https://doi.org/10.1093/europace/eu421>.
  18. Kelly JP, DeVore AD, Wu JJ, et al. Rhythm control versus rate control in patients with atrial fibrillation and heart failure with preserved ejection fraction: insights from get with the guidelines-heart failure. *J Am Heart Assoc* [Internet]. 2019 [cited 2020 Nov 11];8:e011560. Available from: <https://www.ahajournals.org/doi/10.1161/JAHA.118.011560>
  19. Chen S, Dong Y, Fan J, et al. Rate vs. rhythm control in patients with atrial fibrillation - An updated meta-analysis of 10 randomized controlled trials. *Int J Cardiol* [Internet]. 2011 [cited 2020 Dec 10];153:96–98. Available from: <http://www.internationaljournalofcardiology.com/article/S0167527311017207/fulltext>
  20. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* [Internet]. [cited 2020 Dec 10];347:1834–1840. Available from 2002; [www.nejm.org](http://www.nejm.org)
  21. Noheria A, Shrader P, Piccini JP, et al. Rhythm Control Versus Rate Control and Clinical Outcomes in Patients with Atrial Fibrillation: results from the ORBIT-AF Registry. *JACC Clin Electrophysiol*. 2016;2:221–229.
  22. Mujović N, Marinković M, Lenarczyk R, et al. Catheter ablation of atrial fibrillation: an overview for clinicians. *Adv Ther*. 2017;34:1897–1917.
  23. Gupta A, Perera T, Ganesan A, et al. Complications of catheter ablation of atrial fibrillation: a systematic review. *Circ Arrhythm Electrophysiol* [Internet]. 2013 [cited 2020 Dec 9];6:1082–1088. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24243785>
  24. Hussein A, Das M, Riva S, et al. Use of ablation index-guided ablation results in high rates of durable pulmonary vein isolation and freedom from arrhythmia in persistent atrial fibrillation patients. *Circ Arrhythm Electrophysiol* [Internet]. 2018 [cited 2020 Dec 9];11:e006576. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCEP.118.006576>
  25. Packer DL, Mark DB, Robb RA, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA Randomized Clinical Trial. *JAMA*. 2019;321:1261–1274. Available from <https://doi.org/10.1001/jama.2019.0693>.
  26. Noseworthy PA, Gersh BJ, Kent DM, et al. Atrial fibrillation ablation in practice: assessing CABANA generalizability. *Eur Heart J* [Internet]. 2019;40:1257–1264. Available from <https://doi.org/10.1093/eurheartj/ehz085>.
  27. Saglietto A, De Ponti R, Di Biase L, et al. Impact of atrial fibrillation catheter ablation on mortality, stroke, and heart failure hospitalizations: a meta-analysis. *J Cardiovasc Electrophysiol* [Internet]. 2020 [cited 2020 Nov 11];31:1040–1047. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/jce.14429>
  28. Guo J, Nayak HM, Besser SA, et al. Impact of Atrial Fibrillation Ablation on Recurrent Hospitalization: a Nationwide Cohort Study. *JACC Clin Electrophysiol*. 2019;5:330–339.
  29. Bertaglia E, Senatore G, De Michieli L, et al. Twelve-year follow-up of catheter ablation for atrial fibrillation: a prospective, multicenter, randomized study. *Hear Rhythm* [Internet]. 2017 [cited 2020 Nov 8];14:486–492. Available from: <http://www.heartrhythmjournal.com/article/S1547527116312140/fulltext>
  30. Kim M, Yu HT, Kim J, et al. Atrial fibrillation and the risk of ischaemic strokes or intracranial haemorrhages: comparisons of the catheter ablation, medical therapy, and non-atrial fibrillation population. *Eur Eur pacing, arrhythmias, Card Electrophysiol*

- J Work groups Card pacing, arrhythmias, Card Cell Electrophysiol Eur Soc Cardiol 2020.
31. Ding WY, Gupta D. Catheter ablation: the “Pym Particles” of atrial fibrillation? *Europace* [Internet]. 2020; Available from: <https://doi.org/10.1093/europace/euaa299>.
  32. Kim D, Yang P-S, Sung J-H, et al. Less dementia after catheter ablation for atrial fibrillation: a nationwide cohort study. *Eur Heart J* [Internet]. 2020. Available from <https://doi.org/10.1093/eurheartj/ehaa726>.
  33. Marrouche NF, Brachmann J, Andresen D, et al. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* [Internet]. 2018;378:417–427. [cited 2020 Nov 8] Available from: <https://www.nejm.org/doi/10.1056/NEJMoa1707855>.
  34. Noseworthy PA, Van Houten HK, Gersh BJ, et al. Generalizability of the CASTLE-AF trial: catheter ablation for patients with atrial fibrillation and heart failure in routine practice. *Hear Rhythm* [Internet]. 2020 [cited 2020 Aug 22];17:1057–1065. Available from: <https://pubmed.ncbi.nlm.nih.gov/32145348>
  35. Alturki A, Proietti R, Dawas A. et al., Catheter ablation for atrial fibrillation in heart failure with reduced ejection fraction: a systematic review and meta-analysis of randomized controlled trials [Internet]. *BMC Cardiovasc Disord*. BioMed Central Ltd.; 2019 [cited 2020 Nov 14]. p. 18. Available from: <https://bmccardiovascdsord.biomedcentral.com/articles/10.1186/s12872-019-0998-2>
  36. Chen S, Pürerfellner H, Meyer C, et al. Rhythm control for patients with atrial fibrillation complicated with heart failure in the contemporary era of catheter ablation: a stratified pooled analysis of randomized data. *Eur Heart J* [Internet]. 2020;41:2863–2873. Available from <https://doi.org/10.1093/eurheartj/ehz443>.
  37. Kirchhof P, Calkins H. Catheter ablation in patients with persistent atrial fibrillation. *Eur Heart J* [Internet]. 2017;38:20–26. Available from <https://doi.org/10.1093/eurheartj/ehw260>.
  38. Anselmino M, Matta M, D’Ascenzo F, et al. Catheter ablation of atrial fibrillation in patients with left ventricular systolic dysfunction: a systematic review and meta-analysis [Internet]. *Circ Arrhythmia Electrophysiol* Lippincott Williams and Wilkins; 2014 [cited 2020 Dec 10]. p. 1011–1018. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCEP.114.001938>
  39. Gaita F, Scaglione M, Battaglia A, et al. Very long-term outcome following transcatheter ablation of atrial fibrillation. Are results maintained after 10 years of follow up? *Europace* [Internet]. 2018;20:443–450. Available from: <https://doi.org/10.1093/europace/eux008>
  40. Balla C, Cappato R. Atrial fibrillation ablation in heart failure. *Eur Hear J Suppl* [Internet]. 2020 [cited 2020 Nov 13];22:E50–E53. Available from: <https://pmc/articles/PMC7270911/?report=abstract>
  41. Padfield GJ, Steinberg C, Swampillai J, et al. Progression of paroxysmal to persistent atrial fibrillation: 10-year follow-up in the Canadian Registry of Atrial Fibrillation. *Hear Rhythm* [Internet]. 2017 [cited 2020 Dec 10];14:801–807. Available from: <http://www.hearhythmjournal.com/article/S1547527117301492/fulltext>
  42. Nattel S, Guasch E, Savelieva I, et al. Early management of atrial fibrillation to prevent cardiovascular complications. *Eur Heart J* [Internet]. 2014;35:1448–1456. Available from <https://doi.org/10.1093/eurheartj/ehu028>.
  43. Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* [Internet]. [cited 2020 Nov 14];383:1305–1316. Available from: 2020; <https://www.nejm.org/doi/10.1056/NEJMoa2019422>•• **RCT comparing early-rhythm control therapy vs standard therapy in patients with AF.**
  44. Piccini JP, Allred J, Bunch TJ, et al. Rationale, considerations, and goals for atrial fibrillation centers of excellence: a Heart Rhythm Society perspective. *Hear Rhythm* [Internet]. 2020 [cited 2020 Nov 15];17:1804–1832. Available from: <https://doi.org/10.1016/j.hrthm.2020.04.033>.
  45. Bunch TJ, Steinberg BA. Revisiting Rate versus Rhythm Control in Atrial Fibrillation—timing Matters. *N Engl J Med* [Internet]. 2020;383:1383–1384. Available from <https://doi.org/10.1056/NEJMe2027180>.
  46. Cosedis Nielsen J, Johannessen A, Raatikainen P, et al. Radiofrequency ablation as initial therapy in paroxysmal atrial fibrillation. *N Engl J Med* [Internet]. 2012;367:1587–1595. Available from: <https://doi.org/10.1056/NEJMoa1113566>•• **RCT comparing catheter ablation vs AAD as a first-line therapy among patients with paroxysmal AF.**
  47. Wazni OM, Dandamudi G, Sood N, et al. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. *N Engl J Med* [Internet]. 2020. [cited 2020 Dec 10]; Available from <https://www.nejm.org/doi/full/10.1056/NEJMoa2029554>•• **RCT comparing catheter ablation vs AAD as a first-line therapy among patients with paroxysmal AF.**
  48. Andrade JG, Wells GA, Deyell MW, et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. *N Engl J Med* [Internet]. 2020. [cited 2020 Dec 10]; Available from <https://www.nejm.org/doi/full/10.1056/NEJMoa2029980>•• **RCT comparing catheter ablation vs AAD as a first-line therapy among patients with paroxysmal AF.**
  49. Hermida JS, Chen J, Meyer C, et al. Cryoballoon catheter ablation versus antiarrhythmic drugs as a first-line therapy for patients with paroxysmal atrial fibrillation: rationale and design of the international Cryo-FIRST study. *Am Heart J*. 2020;222:64–72. Available from: <http://www.sciencedirect.com/science/article/pii/S0002870319303461>
  50. Vedran V, Nikola P, Gian-Battista C, et al. abstract 13915: cryoballoon catheter ablation versus antiarrhythmic drug as a first-line therapy for patients with paroxysmal atrial fibrillation: results of the cryo-first study. *Circulation* [Internet]. 2020;142:A13915–A13915. Available from [https://doi.org/10.1161/circ.142.suppl\\_3.13915](https://doi.org/10.1161/circ.142.suppl_3.13915).
  51. Chierchia GB, Pavlovic N, Velagic V, et al. Quality of life measured in first-line therapy during the Cryo-FIRST study: a comparison between cryoballoon catheter ablation versus antiarrhythmic drug therapy. *Eur Heart J* [Internet]. 2020;41. Available from <https://doi.org/10.1093/ehjci/ehaa946.0436>.
  52. Kuck K-H, Lebedev DS, Mikhaylov EN, et al. Catheter ablation or medical therapy to delay progression of atrial fibrillation: the randomized controlled atrial fibrillation progression trial (ATTEST). *EP Eur* [Internet]. 2020; Available from: <https://doi.org/10.1093/europace/euaa298>• **RCT assessing the progression of AF among patients with paroxysmal AF treated with catheter ablation vs AAD.**
  53. Sawhney V, Schilling RJ, Providencia R, et al. Cryoablation for persistent and longstanding persistent atrial fibrillation: results from a multicentre European registry. *Europace* [Internet]. 2020 [cited 2020 Nov 9];22:375–381. Available from: <https://academic.oup.com/europace/article/22/3/375/5662413>
  54. Hussein AA, Saliba WJ, Barakat A, et al. Radiofrequency ablation of persistent atrial fibrillation: diagnosis-to-ablation time, markers of pathways of atrial remodeling, and outcomes. *Circ Arrhythmia Electrophysiol* [Internet]. 2016 [cited 2020 Nov 15];9. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCEP.115.003669>
  55. Jones DG, Haldar SK, Donovan J, et al. Biomarkers in Persistent AF and Heart Failure: impact of Catheter Ablation Compared with Rate Control. *Pacing Clin Electrophysiol* [Internet]. 2016 [cited 2020 Nov 15];39:926–934. Available from: <http://doi.wiley.com/10.1111/pace.12919>
  56. Aronsson M, Walfridsson H, Janzon M, et al. The cost-effectiveness of radiofrequency catheter ablation as first-line treatment for paroxysmal atrial fibrillation: results from a MANTRA-PAF substudy. *Europace* [Internet]. 2015;17:48–55. Available from: <https://doi.org/10.1093/europace/euu188>.
  57. Mörtzell D, Arbello E, Dagues N, et al. Cryoballoon vs. radiofrequency ablation for atrial fibrillation: a study of outcome and safety based on the ESC-EHRA atrial fibrillation ablation long-term registry and the Swedish catheter ablation registry. *Europace* [Internet]. 2019;21:581–589. Available from: <https://doi.org/10.1093/europace/euy239>.
  58. Kim YG, Choi J-I, Boo KY, et al. Clinical and echocardiographic risk factors predict late recurrence after radiofrequency catheter



- ablation of atrial fibrillation. *Sci Rep* [Internet]. 2019;9:6890. Available from: <https://doi.org/10.1038/s41598-019-43283-7>.
59. Dretzke J, Chuchu N, Agarwal R, et al. Predicting recurrent atrial fibrillation after catheter ablation: a systematic review of prognostic models. *Europace* [Internet]. 2020;22:748–760. Available from: <https://doi.org/10.1093/europace/eaab041>.
  60. Trines SA, Stabile G, Arbelo E, et al. Influence of risk factors in the ESC-EHRA EORP atrial fibrillation ablation long-term registry. *PACE - Pacing Clin Electrophysiol* [Internet]. 2019 [cited 2020 Dec 15];42:1365–1373. Available from: <https://pubmed.ncbi.nlm.nih.gov/31355938>
  61. Dennis HL, Stanley N, Jonathan MK, et al. Modifiable Risk Factors and Atrial Fibrillation. *Circulation* [Internet]. 2017;136:583–596. Available from: <https://doi.org/10.1161/CIRCULATIONAHA.116.023163>
  62. Nedios S, Kosiuk J, Koutalas E, et al. Comparison of left atrial dimensions in CT and echocardiography as predictors of long-term success after catheter ablation of atrial fibrillation. *J Interv Card Electrophysiol* [Internet]. 2015 [cited 2020 Dec 15];43:237–244. Available from: <https://link.springer.com/article/10.1007/s10840-015-0010-8>
  63. D'Ascenzo F, Corleto A, Biondi-Zoccai G, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. *Int J Cardiol* [Internet]. 2013 [cited 2020 Dec 15];167:1984–1989. Available from: <http://www.internationaljournalofcardiology.com/article/S0167527312006195/fulltext>.
  64. Arbelo E, Brugada J, Blomström-Lundqvist C, et al. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. *Eur Heart J*. 2017;38:1303–1316.
  65. Haeusler KG, Kirchhof P, Endres M. Left atrial catheter ablation and ischemic stroke. *Stroke* [Internet]. [cited 2020 Nov 14];43:265–270. Available from: 2012;.. <https://www.ahajournals.org/doi/10.1161/STROKEAHA.111.627067>
  66. Willems S, Meyer C, De Bono J, et al. Cabins, castles, and constant hearts: rhythm control therapy in patients with atrial fibrillation. *Eur Heart J* [Internet]. 2019;40:3793–3799c. Available from: <https://doi.org/10.1093/eurheartj/ehz782>.
  67. Dinshaw L, Schäffer B, Ö A, et al. Long-term efficacy and safety of radiofrequency catheter ablation of atrial fibrillation in patients with cardiac implantable electronic devices and transvenous leads. *J Cardiovasc Electrophysiol* [Internet]. 2019 [cited 2020 Nov 14];30:679–687. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/jce.13890>
  68. Tilz RR, Heeger CH, Wick A, et al. Ten-Year Clinical Outcome after Circumferential Pulmonary Vein Isolation Utilizing the Hamburg Approach in Patients with Symptomatic Drug-Refractory Paroxysmal Atrial Fibrillation. *Circ Arrhythmia Electrophysiol* [Internet]. 2018 [cited 2020 Nov 14];11. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCEP.117.005250>
  69. Buchta P, Sierpiński R, Myrda K, et al. New hope for patients and challenges for the multidisciplinary arrhythmia team: a hybrid convergent approach for atrial fibrillation treatment. *Kardiol Pol*;2020. doi: 10.33963/KP.15640
  70. Berger WR, Meulendijks ER, Limpens J, et al. Persistent atrial fibrillation: a systematic review and meta-analysis of invasive strategies. *Int J Cardiol* [Internet]. 2019 [cited 2020 Nov 14];278:137–143. Available from: <https://doi.org/10.1016/j.ijcard.2018.11.127>.
  71. Swaans MJ, Post MC, Rensing BJWM, et al. Ablation for atrial fibrillation in combination with left atrial appendage closure: first results of a feasibility study. *J Am Heart Assoc*. 2012; 1: doi:10.1161/JAHA.112.002212
  72. Phillips KP, Romanov A, Artemenko S, et al. Combining left atrial appendage closure and catheter ablation for atrial fibrillation: 2-year outcomes from a multinational registry. *Europace* 2020;22:225–231.
  73. Kotalczyk A, Mazurek M, Kalarus Z, et al. Stroke prevention strategies in high-risk patients with atrial fibrillation. *Nat Rev Cardiol* [Internet]. 2020; Available from: <https://doi.org/10.1038/s41598-020-00459-3>.
  74. Gorenek (Chair) B, Halvorsen S, Kudaiberdieva G, et al. Atrial fibrillation in acute heart failure: a position statement from the Acute Cardiovascular Care Association and European Heart Rhythm Association of the European Society of Cardiology. *European Heart Journal: Acute Cardiovascular Care*. 2020 [cited 2020 Nov 11];9:348–357. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/31976747>
  75. Brandes A, Crijns HJGM, Rienstra M, et al. Cardioversion of atrial fibrillation and atrial flutter revisited: current evidence and practical guidance for a common procedure. *Europace* [Internet]. 2020;22:1149–1161. Available from: <https://doi.org/10.1093/europace/eaab057>.
  76. Cho Y, Oh I-Y, Park JJ, et al. Impact of successful restoration of sinus rhythm in patients with atrial fibrillation and acute heart failure: results from the Korean Acute Heart Failure registry. *Cardiology Journal*. 2020. Available from <https://doi.org/10.5603/CJ.a2020.0103>.
  77. Airaksinen KEJ. Early versus delayed cardioversion: why should we wait? [Internet]. Expert Review of Cardiovascular Therapy. Taylor and Francis Ltd; 2020 [cited 2020 Nov 13]. p. 149–154. Available from: <https://www.tandfonline.com/doi/abs/10.1080/14779072.20201736563>
  78. Gorenek B, Pelliccia A, Benjamin EJ, et al. European Heart Rhythm Association (EHRA)/European Association of Cardiovascular Prevention and Rehabilitation (EACPR) position paper on how to prevent atrial fibrillation endorsed by the Heart Rhythm Society (HRS) and Asia Pacific Heart Rhythm Society (APHRS). *Eur J Prev Cardiol* [Internet]. 2017 [cited 2020 Nov 11];24:4–40. Available from: <http://journals.sagepub.com/doi/10.1177/2047487316676037>
  79. Javed S, Gupta D, Lip GYH. Obesity and atrial fibrillation: making inroads through fat. *Eur Heart J - Cardiovasc Pharmacother* [Internet]. 2020; Available from: <https://doi.org/10.1093/ehjcvp/pvaa013>.
  80. Lip GYH, Merino JL, Banach M, et al. Clinical factors related to successful or unsuccessful cardioversion in the Edoxaban versus warfarin in subjects Undergoing cardioversion of Atrial Fibrillation (ENSURE-AF) randomized trial. *J Arrhythmia*. 2020;36:430–438. [cited 2020 Nov 13. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1002/joa3.12341>
  81. Middeldorp ME, Pathak RK, Meredith M, et al. PREVENTion and reverse Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. 2018. EP Europace. 20:1929–1935. Available from: <https://doi.org/10.1093/europace/euy117>.
  82. Rienstra M, Hobbelt AH, Alings M, et al. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: results of the RACE 3 trial. *Eur Heart J* [Internet]. 2018;39(32):2987–2996. Available from: <https://doi.org/10.1093/eurheartj/ehx739>
  83. Bhardwaj R, Koruth JS. Novel ablation approaches for challenging atrial fibrillation cases (mapping, irrigation, and catheters). *Cardiology Clinics*. 2019;37:207–219. Available from: <http://www.sciencedirect.com/science/article/pii/S0733865119300128> 2
  84. Rottner L, Bellmann B, Lin T, et al. Catheter ablation of atrial fibrillation: state of the art and future perspectives. *Cardiovascular Therapy*. 2020; 9:45–58. Available from: <https://doi.org/10.1007/s40119-019-00158-2>.
  85. Aj G, Jean C, Marc D, et al. Cryoballoon or Radiofrequency Ablation for Atrial Fibrillation Assessed by Continuous Monitoring. *Circulation* [Internet]. 2019;140:1779–1788. Available from <https://doi.org/10.1161/CIRCULATIONAHA.119.042622>.
  86. Kuck K-H, Brugada J, Fürnkranz A, et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med* [Internet]. 2016;374(23):2235–2245. Available from.
  87. Manolis AS. Ablation of atrial fibrillation: single-shot techniques poised to dominate rhythm control strategies/the future is here [Internet]. *Journal of Thoracic Disease*. AME Publishing Company;

- 2017 [cited 2020 Nov 15]. p. E313–E321. Available from ;9(3);/pmc/articles/PMC5394036/?report=abstract
88. Bellmann B, Lin T, Ruppersberg P, et al. Identification of active atrial fibrillation sources and their discrimination from passive rotors using electrographical flow mapping. *Clinical Research in Cardiology*. 2016;374(11):1021–1032. Available from. .
  89. Bellmann B, Zettwitz M, Lin T, et al. Velocity characteristics of atrial fibrillation sources determined by electrographic flow mapping before and after catheter ablation. *International Journal of Cardiology* [cited 2020 Nov 15];383:56–60. Available from 2020; <http://www.internationaljournalofcardiology.com/article/S0167527318368992/fulltext>
  90. Koruth JS, Kuroki K, Kawamura I, et al. Focal pulsed field ablation for pulmonary vein isolation and linear atrial lesions: a preclinical assessment of safety and durability. *Circ Arrhythmia Electrophysiol* [Internet]. 2020 [cited 2020 Nov 13];13:514–528. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCEP.120.008716>
  91. Bradley CJ, Haines DE. Pulsed field ablation for pulmonary vein isolation in the treatment of atrial fibrillation. *Journal of Cardiovascular Electrophysiology*. [cited 2020 Nov 13];31:2136–2147. Available from. 2020;(8):. <https://onlinelibrary.wiley.com/doi/abs/10.1111/jce.14414>
  92. Reddy VY, Neuzil P, Koruth JS, et al. Pulsed field ablation for pulmonary vein isolation in atrial fibrillation. *J Am Coll Cardiol*. 2019;74(3):315–326.
  93. Perez MV, Mahaffey KW, Hedlin H, et al. Large-scale assessment of a smartwatch to identify atrial fibrillation. *N Engl J Med* [Internet]. [cited 2020 Apr 28];381:1909–1917. Available from. 2019;(20): <http://www.nejm.org/doi/10.1056/NEJMoa1901183>.
  94. Turakhia MP, Desai M, Hedlin H, et al. Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: the apple heart study. *Am Heart J*. 2019;207:66–75.
  95. Guo Y, Wang H, Zhang H, et al. Mobile photoplethysmographic technology to detect atrial fibrillation. *J Am Coll Cardiol*. 2019;74(19):2365–2375.
  96. Giada F, Gulizia M, Francese M, et al. Recurrent Unexplained Palpitations (RUP) study comparison of implantable loop recorder versus conventional diagnostic strategy. *J Am Coll Cardiol*. 2007;49:1951–1956.
  97. Sanna T, Diener H-C, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* [Internet]. [cited 2020 Aug 23];370:2478–2486. Available from. 2014;(26) <http://www.nejm.org/doi/10.1056/NEJMoa1313600>.
  98. Guo Y, Lane DA, Wang L, et al. Mobile Health (mHealth) technology for improved screening, patient involvement and optimising integrated care in atrial fibrillation: the mAFA (mAF-App) II randomised trial. *Int J Clin Pract* [Internet]. 2019 [cited 2020 May 16];73. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.1111/ijcp.13352>
  99. Andrade JG, Deyell MW, Verma A, et al. Association of atrial fibrillation episode duration with arrhythmia recurrence following ablation: a secondary analysis of a randomized clinical trial. 2020. *JAMA Network Open*. ;3 e208748–e208748. Available from. (7):. <https://doi.org/10.1001/jamanetworkopen.2020.8748>.
  100. Kim M, Hong M, Kim JY, et al. Clinical relationship between anemia and atrial fibrillation recurrence after catheter ablation without genetic background. *IJC Hear Vasc*. 2020;27:100507.
  101. Yanagisawa S, Inden Y, Kato H, et al. Impaired renal function is associated with recurrence after cryoballoon catheter ablation for paroxysmal atrial fibrillation: a potential effect of non-pulmonary vein foci. *J Cardiol* [Internet]. 2017 [cited 2020 Sep 28];69:3–10. Available from: <http://dx.doi.org/10.1016/j.jjcc.2016.08.002>.
  102. Li M, Liu T, Luo D, et al. Systematic review and meta-analysis of chronic kidney disease as predictor of atrial fibrillation recurrence following catheter ablation. *Cardiol J* [Internet]. 2014 cited 2020 Sep 28;21:89–95. Available from: [www.cardiologyjournal.org](http://www.cardiologyjournal.org)
  103. Deng H, Shantsila A, Xue Y, et al. Renal function and outcomes after catheter ablation of patients with atrial fibrillation: the Guangzhou atrial fibrillation ablation registry. *Arch Cardiovasc Dis*. 2019;112:420–429.
  104. Guhl E, Althouse AD, Pusateri AM, et al. The Atrial Fibrillation Health Literacy Information Technology Trial: pilot Trial of a Mobile Health App for Atrial Fibrillation, JMIR cardio [Internet]. 2020 cited 2020 Nov 14;4:e17162. Available from, ; . ., <http://www.ncbi.nlm.nih.gov/pubmed/32886070>,1
  105. Chao T-F, Liao J-N, Tuan T-C, et al. Incident co-morbidities in patients with atrial fibrillation initially with a cha2ds2-vasc score of 0 (males) or 1 (females): implications for reassessment of stroke risk in initially 'low-risk' patients, Thrombosis and Haemostasis. 2019 cited 2020 Dec 8;119:1162–1170. Available from: <http://www.thieme-connect.de/DOI/DOI?10.1055/s-0039-1683933>
  106. Kotalczyk A, Kalarus Z, Wright DJ, et al., cardiac electronic devices: future directions and challenges. *Medical Devices: Evidence and Research*. Dove Medical Press Ltd; 2020 cited 2020 Oct 25. p. 325–338. Available from: /pmc/articles/PMC7526741/?report=abstract 13